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Ultrafast imaging of cardiac electromechanical wave propagation with volumetric optoacoustic tomography

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ABSTRACT

Understanding the mechanisms of cardiac disorders largely depends on availability of multi-dimensional and multi-parametric imaging methods capable of quantitative assessment of cardiac morphology and function. The imaging modalities commonly employed in cardiac research, such as ultrasonography and magnetic resonance imaging, are lacking sufficient contrast and/or spatio-temporal resolution in 3D in order to reveal the multi-scale nature of rapid electromechanical activity in a beating heart. Our recently developed volumetric optoacoustic tomography (VOT) platform offers versatile observations of the heart function with rich optical contrast at otherwise unattainable temporal and spatial resolutions. Herein, we further advance the imaging performance by developing compressed acquisition scheme to boost the temporal resolution of VOT into the kilohertz range, thus enabling 3D mapping of electromechanical wave propagation in the heart. Experiments in isolated mouse hearts were performed by exciting the entire imaged tissue volume with nanosecond-duration laser pulses at 1 kHz repetition rate pulse operating at 532 nm and sparse tomographic signal sampling using a custom-made 512-element spherical matrix ultrasound array. By analyzing the strain maps obtained from the rapid VOT image sequence, it was possible to quantify the phase velocity of the electromechanical cardiac waves, in good agreement with previously reported values.

Keywords: Optoacoustic tomography, photoacoustics, ultrafast volumetric imaging, isolated heart, Langendorff, electromechanical cardiac wave

1. INTRODUCTION

Irregular cardiac electrical activity is known to be a fundamental source of arrhythmic events. Research efforts have been devoted since the beginning of the 20th century to unravel the basic mechanisms behind this phenomenon [1, 2]. While measurements of cardiac tissue electrical activity at the single cell level have been advanced over time, these approaches are still not capable of characterizing heart function on a macroscopic level [3]. Being able to map electrocardiogram (ECG) signals has facilitated determining the origin and propagation paths of arrhythmic events in different regions of the heart [4]. This information can be combined with the high-resolution anatomical images obtained with clinical imaging modalities, which however suffer from low temporal resolution and are incapable to visualize the cardiac dynamics [5]. So far, ultrafast ultrasound (US) imaging has been the only modality with the potential to characterize the multi-scale nature of cardiac function by visualizing the electromechanical wave propagation in the heart at very high spatial and temporal resolution both in living animals and in the isolated Langendorff heart model [6,7].

The Langendorff heart model is based on isolating this organ from the animal's body and perfusing it in a retrograde fashion via the aorta. It found large applicability in studies of cardiac function and electrophysiology as it avoids the complexity of *in-vivo* experiments and further facilitates studying cardiovascular diseases by investigating the heart as an organized structure [8,9] as well as revealing the sources of cardiac arrhythmias [7]. A combination of US and optical imaging has been shown to exploit the unique properties of optical contrast and US resolution to resolve the spatio-temporal dynamics of scroll waves and filament-like phase singularities during arrhythmic events induced in the isolated Langendorff heart [7]. The same synergetic combination of optics and US is exploited in optoacoustic (OA, photoacoustic) imaging, which is growingly been used in cardiovascular biology and other fields [10-15]. Recently, we have demonstrated that the entire Langendorff-perfused mouse heart can be imaged volumetrically with

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a custom-made volumetric OA tomography (VOT) system providing a unique combination of fast volumetric imaging speed and depth [16]. On the other hand, we have shown that the frame rate achieved with VOT can be significantly accelerated with a compressed acquisition scheme that consists in selecting only a small number of randomly distributed sensors for each laser shot [17]. Herein we implemented the compressed acquisition scheme to reach a temporal resolution in the sub-millisecond range with a VOT system custom-designed for efficient imaging of Langendorff hearts, ultimately aiming at visualizing the propagation of electromechanical waves.

2. METHODS AND RESULTS

2.1. Langendorff preparation

The Langendorff heart model enables keeping cell activity for several hours by delivering oxygen and nutrients through the coronary arteries while preserving the temperature and pH at the physiological range of the animal's body [18]. Specifically, the oxygenated perfusate (Tyrode's solution) was pumped through a cannula inserted in the ascending aorta and fixed using a black-braided suture. Retrograde perfusion permanently closes the aortic valve and allows the perfusate to flow into the coronary microvasculature. An 8-week-old female CD1 mouse hearts were harvested and imaged in the experiments. Image acquisition was started 10-20 minutes after transferring the heart to the imaging system to ensure that it recovered back to its physiological range, the beating cycle was stabilized and the remaining blood in the heart was completely removed.

2.2. Volumetric optoacoustic tomography setup

The cannulated heart was horizontally suspended in a custom-made VOT platform (Fig. 1a). OA signal acquisition was accomplished by accommodating a custom-made spherical transducer array, placed beneath the heart, in an *ad-hoc* designed sample chamber. The sample chamber was perfused with Tyrode's solution to provide acoustic coupling as well as to maintain the temperature and pH level (superfusion) [16]. The spherical transducer array is composed of 512 piezocomposite elements (10 MHz central frequency, ~100% -6 dB detection bandwidth) arranged into a spherical surface of the transducer with and angle of 140° (1.3π solid angle). The effective field of view provided by the transducer array is approximately 6x6x6 mm^3, where an almost isotropic resolution of approximately 75 μm is achieved around the center of the sphere [19]. Light excitation for OA signal excitation was provided by a custom-made fiber bundle with 7 outputs that illuminates the heart homogeneously covering the entire volume. All 7 output ferules of the fiber bundle were directed towards the center of the transducer array. The total energy per pulse measured at the output of the fiber bundle was approximately 1 mJ/cm^2. The laser source used for illuminating the heart was a frequency-doubled Q-switched diode laser providing ~10 ns duration light pulses at 532 nm (EdgeWave GmbH, Würselen, Germany). The per-pulse energy and the pulse repetition frequency (PRF) of the laser were set to 4 mJ and 1.6 kHz, respectively.

2.3. Data acquisition

OA signals corresponding to the time-resolved pressure values at the elements of the transducer array were digitized at 40 megasamples per second with a custom-made data acquisition system (Falkenstein Mikrosysteme GmbH, Taufirchen, Germany). An imaging rate of 1.6 kHz was accomplished by acquiring only a set of signals for each laser pulse. Specifically, 16 randomly distributed groups of array elements were considered (Fig. 1b). The signals for all elements of each group were simultaneously acquired for each laser pulse, while different groups were sequentially acquired for subsequent pulses. Signal acquisition was triggered with the Q-switch output of the laser. Each time-resolved signal consisted of 496 samples delayed by 14.925 μs with respect to the laser emission time points. In each experiment, 16000 consecutive frames were recorded, corresponding to a total acquisition duration of 10 s. The acquired data was transmitted to a PC via Ethernet at a rate of ~485 Mbit/s.

2.4. Optoacoustic image reconstruction

Three-dimensional (3D) OA images were reconstructed from the sparsely acquired signals with a model-based (iterative) reconstruction method previously described in [17]. Basically, discretization of the forward OA model was

performed to derive an algebraic equation where a pressure vector p_i representing the OA signals for the transducer elements acquired for the i-th frame and for all time points considered is expressed as

$$p_i = C_i A h_i \tag{1}$$

where h_i is the absorbed light energy for a grid of points enclosing the imaged object, expressed in a vector form, for the i-th frame. A is the OA model matrix mapping optical absorption to pressure signals at the locations of the transducer elements. The calculation of matrix A is described in detail in [20]. C_i is the subsampling matrix corresponding to the active elements for the i-th frame. Considering a sequence of l frames, the corresponding algebraic models can be combined as

$$\mathrm{p} = \mathrm{C}\mathrm{A}_{tot} h \tag{2}$$

where $\mathrm{p} = (\mathrm{p}_1, \mathrm{p}_2, ..., \mathrm{p}_n)^T$, $\mathrm{C} = \mathrm{diag}(\mathrm{C}_1, \mathrm{C}_2, ..., \mathrm{C}_n)$, $\mathrm{A}_{tot} = (\mathrm{I}_n \otimes \mathrm{A})$ - being I_n the n by n identity matrix - and $h = (\mathrm{h}_1, \mathrm{h}_2, ..., \mathrm{h}_n)^T$. The matrix C corresponding to randomly selected channels is highly likely to verify the restricted isometry property (RIP) required for accurate compressed-sensing based reconstruction. Thereby, the inversion problem to simultaneously reconstruct the entire sequence was defined as

$$h = \underset{h'}{\operatorname{argmin}} \left\{ \frac{1}{2} \| p_m - CAh' \|_2^2 + \lambda \cdot ICTV(h') \right\} \tag{3}$$

where $\frac{1}{2} \| p_m - CAh' \|_2^2$ is the fidelity term and $TV(h')$ is a total variation regularization term.

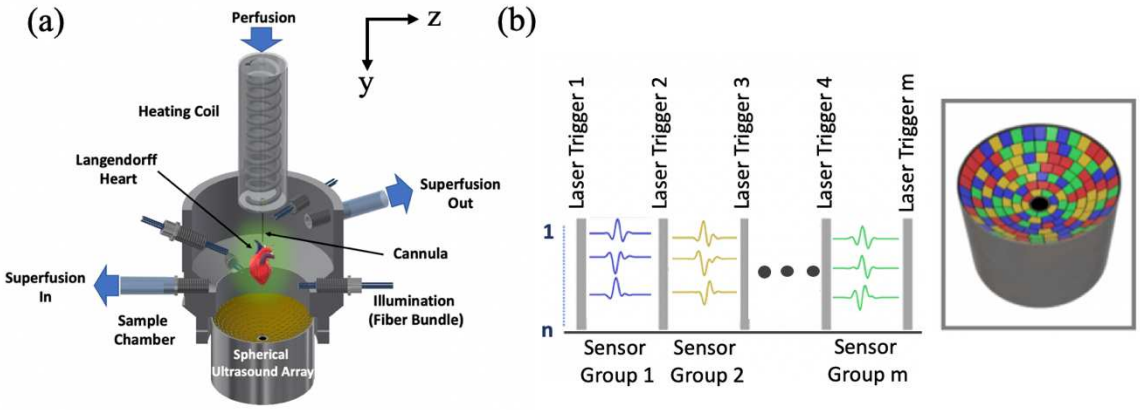

Figure 1. OA imaging of the Langendorff heart with sparse data acquisition and model-based reconstruction. (a) Real-time VOT setup used to efficiently capture the isolated heart. (b) OA data acquisition scheme consisting of m randomly distributed groups of 512/m array elements subsequently acquired for each laser pulse.

2.5. Phase analysis

Phase analysis was introduced as a method to analyze the spatio-temporal changes in the myocardium during cardiac fibrillation depending on the activation pattern [21]. These spatio-temporal changes contain information on the complex mechanisms of cardiac arrhythmias and can be mapped by deploying electrical or optical measurements using interpolated electrodes [22] as well as voltage or calcium imaging methods [23]. Visualizing the 3D dynamics is essential to elucidate the mechanisms of cardiac fibrillation. It has been recently shown that the core of vortex-like rotating waves, phase singularities, and mechanical filaments can be visualized using combined optical and US imaging on a Langendorff-perfused pig heart during ventricular fibrillation [7]. In this work, we implemented the phase mapping method on the four-dimensional (4D) OA data acquired from a healthy Langendorff-perfused mouse. The anatomy of the Langendorff isolated heart is presented in two maximum intensity projections (MIPs) of the 3D OA image in Figs. 2a and 2b. The red line in Fig. 2a corresponds to the slice used to calculate the phase map shown

in Figs. 2c. The color bar represents the phase value (normalized between 0 and 1.2 radians), while the amplitude at each pixel is encoded as the brightness in the image. Black lines depict the isochrone curves and the arrows show the wave propagation direction. Phase maps were created offline following OA data acquisition. First, the absorption change over time of each voxel was tracked. Then, Fourier analysis was implemented to extract the frequency information on a per-voxel basis. Subsequently, fundamental and harmonic frequencies of the heartbeat were extracted for further analysis. Given that the heart beats regularly and in a cyclical manner, this analysis highlights the voxel value changes at the interfaces between the heart wall and the fluids occupying space inside or outside of the heart.

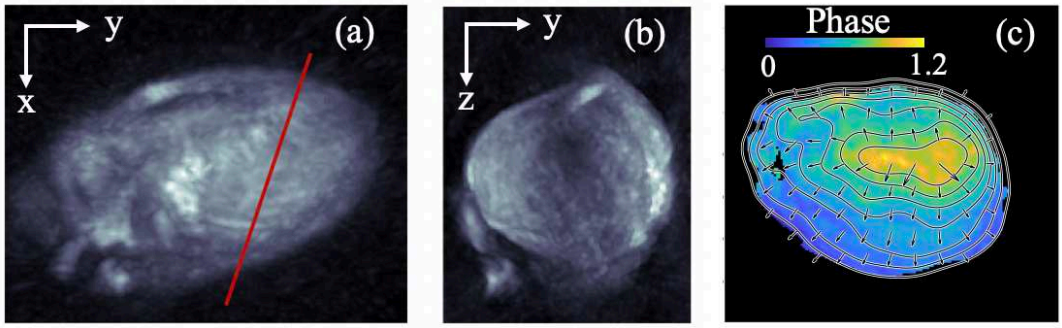

Figure 2. Phase mapping of the electromechanical wave in the heart. (a) MIP along the z direction of the reconstructed 3D image of the Langendorff isolated heart. (b) MIP along the z direction of the reconstructed 3D image of the Langendorff isolated heart. (c) Phase map for the slice indicated in (a).

3. DISCUSSION

Mapping tissue deformation in the entire heart with a spatio-temporal resolution in the <100-micrometer and kilohertz range can massively advance our understanding of the propagation of electromechanical waves at the tissue level. Currently, no imaging modality provides sufficient temporal resolution for 3D imaging with sufficient contrast to reliably characterize the electromechanics of the heart. OA offers the unique capability to simultaneously cover the entire Langendorff-perfused heart with a single laser pulse, thus facilitating high frame-rate imaging [16]. The versatile optical contrast across multiple spatial and temporal scales provided by OA enables resolving the dynamics of optical probes that can measure functional parameters, e.g. voltage and calcium sensors, in the whole heart and other organs, hence enabling unprecedented opportunities in biomedical research [24]. OA tomography is also significantly more quantitative than diffuse optical methods. Accurate OA images can be obtained if sufficient tomographic angular coverage is provided, which is ensured with the spherical arrangement of elements of the transducer array employed in this study.

In the heart, electric and mechanical mechanisms are coupled at the cellular level, although the corresponding waves have fundamentally different nature. The synchronized motion of the cardiac tissue can be altered in some disease conditions. It has recently been shown that electrical and mechanical phase singularities in vortex-like scroll waves in ventricular fibrillation and ventricular tachycardia coexist [7]. However, the dynamics of electro-mechanical wave coupling in the excitable and deformable cardiac tissue is still not fully understood. We believe that the methodology described in this work can shed some light into these mechanisms.

4. CONCLUSION

Development of ultra-fast multiparametric imaging methods is key to unraveling the mechanisms of arrhythmia and other cardiac disorders. Herein, we developed an ultrafast compressed sensing approach for cardiac OA imaging at kilohertz volumetric frame rates. We have shown that OA tomography is capable of offering a unique combination between rich optical contrast, fast 3D imaging speed and deep tissue penetration not reachable with other modalities. We believe that the capabilities of the showcased imaging technique will serve as a powerful tool for studying electromechanical phenomena in the heart in health and disease at multiple spatial and temporal scales.

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